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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/585,475	06/02/2000	N. Leigh Anderson	40488	6582

7590 05/23/2005

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EXAMINER	
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ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/585,475	ANDERSON ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *85-94 and 96-111* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *85-94 and 96-111* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Replay to Notice of Non-compliant amendment filed January 24, 2005 is acknowledged. Claims 1-84 were previously canceled; claim 95 has been currently canceled. Claims 85, 88, 98 and 101 have been amended and new claims 106-111 have been added. Claims 85-94 and 96-111 are pending in the application and are the subject of this Office Action.

Office Action

1. Objections

1.1. Specification

The examiner withdraws the objection to the term abundance, because the use of the term in the disclosure is in accord with its use in the art. The specification, however, is objected to for lack of definition of the term "derivatization status", specification, page 7, line 31.

In response to this objection Applicants argue, "The terms do not require a separate definition, as they are understood in the art. Furthermore, the meaning of the terms is further elaborated on at several locations in the specification itself including a location two paragraphs later"

This argument of Applicants has been fully considered but is found not persuasive for the following reasons. The term "derivatization status" is not defined by the specification. There are many ways to make a derivative of a protein, for that reasons the term "derivatization status" in not understood in the art without providing a further explanation of what kind of derivative one is referring to.

Two paragraph later, page 8, line 13 of the specification, one reads:

" A 'level' refers to abundance, derivatization status, protein variant presence, concentration, chemical or biological activity, which is detectable. An 'altered level' refers to a change in the 'level' when compared to a different sample. The level may be an actual measured amount of a protein but is generally a 'relative level' of a protein compared to the 'level' of other proteins or standards, which may be run in the same batch."

In the above passage Applicants define the term "level" by indefinite term "derivatization status". Thus, the passage does not elaborate on the meaning of the terms "derivatization status". In summary, the objection is not withdrawn.

1.2. Claims

Objections to claims 14-84 and to claims 88 and 101 made in the Office Action of August 12, 2004 are withdrawn, because the claims have been amended.

New claim 106 contains a typographical error in line 12. The error was previously present in other claims.

The marker methionine adenosyltransferase is spelled throughout the claims incorrectly as "methionine adensyltransferase"

2. Rejections

2.1 35 USC, section 112, second paragraph

Rejection of claim 98 for lack of antecedent for "the abundance" is withdrawn, because the claim has been amended. All other rejections made under this paragraph in the Office Action of August 12, 2004 are maintained and repeated herein.

Claim 85-94 and 96-111 are rejected for the use of terms "a degree of effective response", "a degree of toxicity" and "a degree of efficacy" of an agent, because neither the claims nor the specification define the term efficacy, toxicity or the term effective response. As indicated in the previous Office Actions it is unknown to what the word efficacy is related. Is this an efficacy of a drug in the treatment of a particular disorder? How the degree of efficacy is defined? It is unknown what toxicity are Applicants referring to. The disclosure is silent as to whether Applicants mean hephatotoxicity, nephrotoxicity, myotoxicity, toxicity to central nervous system, developemental toxicity, genetic toxicity, inhibition of proliferation, inhibition of clonogenicity, intactness of cell membranes, or apoptosis? And how to measure them? Toxicologists use a battery of about 10 tests to fully characterize toxicity of an agent. The indefinite terms and phrases render the claims indefinite.

Claim 85 recites the limitation "effective response", which is indefinite, because neither the claim nor the specification defines what the response must be effective for.

Claims 88 and 101 recite the phrase "relative amount of toxicity or effectiveness", which is confusing. Relative to what?

Claim 88 is also confusing because it is not clear to what levels the claim is referring to.

Claims 96-97 and 104 recite the terms "effective amount" and "greater then effective amount", which are not defined by the claim or specification. The claims and specification do not define what the amount must be effective for. Furthermore, the term "greater" is relative which renders the claims indefinite. The term "greater" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 96, in addition, recites in the second line the phrase "an amount greater than an effective amount of an agent" which is indefinite. It is not clear to what the Applicants are referring to, i.e., an amount of what?

Claims 97, 105, and 104 are also unclear because it is not known to amount of what the Applicants are referring to in the phrases "the greater amount" and "an amount greater than".

Claim 98 is rejected because it is not clear in comparison with what the abundance is significantly different. The examiner assumes, for examination purposes, the level of said marker protein is significantly different from the one observed in nontreated control or after treatment with a known agent.

New claims 106-111 are rejected as indefinite because they recite the phrases

1) "a degree of toxicity or efficacy of an agent" (see above) , and

2) at least one polypeptide fragment (a polypeptide fragment of what?),

which are indefinite. Indefinite recitations render the claims indefinite.

Claim 111 is unclear for missing a fragment of text after the word "said" in the second line.

In their REMARS on page 12, third paragraph and further, Applicants traverse the rejection of claims 85, 94 and 96-105 for use of indefinite terms

1) a degree of efficacy,

2) a degree of effective response,

3) effective response, and

4) relative amount of toxicity or effectivness,

stating:

> "It will be appreciated that all compounds are toxic to biological systems at some amount. The recognition of toxicity is also a well-understood concept. Likewise, well-established effective drugs (or other bioaffecting agents) are only effective when used in sufficient amounts. It will be appreciated that certain low amounts of toxicity may be acceptable and certain low amounts of efficacy are NOT acceptable. All claims involve comparing the marker(s) (or fragments) in a test sample to the same in a control sample or other sample exposed to a known toxic or a known effective agent. Within this context, the objected to terms are appropriately used."

Applicants' arguments have been considered but are found not persuasive for the following reasons.

The fact that all compounds are toxic at some amounts does not explain what is the meaning of the term "relative toxicity" used by the claims.

b) It is not understandable what Applicants mean saying "the recognition of toxicity is also a well-understood concept." Recognition of toxicity is not a concept, it is a recognition. The term "toxicity", without a definition, is a vague concept that cannot be used for quantification of any toxic effect. If toxicity is a well-understood concept why Applicants do not present the concept explicitly? The specification is silent as to which toxic effects Applicants are referring to.

c) The fact that "well-established effective drugs are only effective when used in sufficient amounts" although true, does not explain any of the terms listed under 1)-4) above.

d) The notion that "certain low amounts of toxicity may be acceptable and certain low amounts of efficacy are NOT acceptable" is a prerequisite of any pharmacological treatment, however, it does not define any of the terms listed under 1)-4) above.

e) Furthermore, It is not clear what Applicants mean by the term "fragment", which is given in parenthesis.

f) All claims involve comparing the markers in a test sample to the same in control or other sample exposed to a known toxic or a known effective agent. This comparison allows to state whether there is more or less of the marker after the treatment than in control or in a sample treated with a known effective agent. The comparision allows to

disclose new markers. The comparison, however, does not allow to define the terms listed under 1)-4) above.

2.2. 35 USC section 112, first paragraph

2.2.1. Lack of written description

New claims 106-111 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are directed to detecting

1) any at least one polypeptide fragment of markers listed in claim 106,

2) any plural fragments of said markers,

3) any fragment from a plurality of said markers.

Neither the specification nor claims as originally filed refer to any fragment of any marker they teach. On page 63 of the Applicants write how they identified spots in proteome. They did it, among others, by determination molecular mass of digested polypeptides and protein fragment ions, or by sequencing fragments of protein form a spot. Nowhere the Inventors used fragments of proteome proteins as markers. Claim 106-111 introduce, therefore, **new matter**, and one skilled in the art concludes Applicants were not in possession of the claimed invention at the time the Application was filed. Thus, claims 106-111 are rejected.

Claims 85-94, 96-105 and new claims 106-111 are rejected for lack of written description for the reasons explained in earlier Office Actions and elaborated bellow under A, B, and C.

A. The claims are directed to a method for determining a degree of toxicity or efficacy **to any agent**, i.e., including any agent that may act on living organism, i.e. according to the definition of page 8, line 5,"any chemical, physical, biological, electrical or radiation treatment which is capable of modifying the abundance of the protein marker." Thus, the claims are directed to determining the toxicity or efficacy of a genus of agents, for which there is no sufficient description in the specification or in claims. The Applicants teach statistically significant changes in some proteins present in the proteome of rat liver, wherein the changes are induced by **antilipemic agents** including

pravastatin,

fluvastatin,

probusol,

simvastatin,

lovastatin,

cholestyramine,

cholestyramine plus lovastatin; see page 58 and see also Tables 1-3. Table 1 uses trademark names of seven antilipemic agents, one of which is lovosatin (Mevracor). In addition, the first paragraph of the Summary of Inventions reads "the object of the present invention is the determination the degree of efficacy and potential toxicity resulting from administration of an *antilipemic agent* [Emphasis added; not any

agent but only antilipemic.] by detection and/or quantification of at least one protein marker indicative of drug toxicity or efficacy in a biological sample". This passage provides evidence the Applicant's intention is not to determine the toxicity or efficacy of any agent.

Applicants treat lovastatin as a well known antilipemic agent and state on page 30, "other antilipemic agents produced similar results". Similar, however, is a relative term. Similar does not mean the same or representative, i.e. identifying specific characteristics. Table 1 presents 136 MSNs that are expressed at the level singnificantly different in treated sample, at the $p<0.005$, than in control. The inspection of the data reveals that there are only 3 out of 138 MSNs (2.17% of markers recorded), i.e., MSN 162 D-dopachrome tautomerase, MSN362 (not indentified in Table 1) and MSN413, which is cytosolic synthase of HMG-CoA, that are significantly changed in 5 out of 7 (71.4%) antilipemic agents. Thus, even these three markers could not be used in the claimed assay for 7 antilipemic drugs taught by Applicants. Therefore, changes in proteome induced by lovstatin cannot be representative of the changes induced by other antilipemic drugs, not to speak of any other agents. None of antilipemic drugs, nor all of them, can be used as representative of other chemical and physical agents when it comes to the changes induced in proteome. In conclusion, changes in the proteome disclosed after treatment with the listed antilipemic agents are not representative of the changes induced by any agents, and such changes cannot be applied in a method broadly claiming determination of toxicity and efficacy for any agent, or any antilipemic drug. For that matter one skilled in the art is not convinced

that Applicants were iln possession of the claimed invention when the application was filled.

B. The claims are directed a method of determination of degree of toxicity or efficacy of an agent in any tissue of interest. The term "tissue of interest" is a generic term that covers many tissues in any animal, i. e. liver tissue, stomach tissue, gut tissue, kidney tissue, central nervous system tissue, embryonic tissues, and others, whereas Applicants use only rat liver for which obtaining a proteome is the best established. The expression of proteins in rat liver is not a representative of expression of proteins in all tissues as broadly claimed. Not all markers present in rat liver proteome are present in proteomes from other tissues. Such proteomes and their changes caused by any agent, or any antilipemic agent, are not taught by Applicants. For that matter one skilled in the art is not convinced that Applicants were in possession of the claimed invention when the application was filled.

C. The specification fails to describe the terms "a degree of toxicity" and/or "a degree of efficacy". The disclosure is silent as to what Applicants mean by the term toxicity. Do Applicants mean for example, hephatotoxicity, nephrotoxicity, myotoxicity, toxicity to central nervous system, developemental toxicity, genetic toxicity, inhibition of proliferation, inhibition of clonogenicity, intactness of cell membranes, or apoptosis? Because the description of toxicity and efficacy is lacking, Applicants do not teach any standards of determination whether a tested agent is toxic or efficient. Toxicologists use

a battery of about 10 tests to characterize toxicity of an agent. Applicants disclose none. Which of the routine tests used by toxicologist is correlated with appearance/disappearance of a particular marker in dependence on dose of an agent? Furthermore, Applicants attention is turned out to the fact that although the first paragraph of the Summary of Inventions states "the object of the present invention is the determination the degree of efficacy and *potential toxicity* [Emphasis added; the term toxicity is not described and the term "potential toxicity" is even more vague.] resulting from administration of an antilipemic agent by detection and/or quantification of at least one protein marker indicative of drug toxicity or efficacy in a biological sample", the objective has not been achieved by Applicants because no such marker has been identified. For that matter one skilled in the art is not convinced that Applicants were in possession of the claimed invention when the application was filled.

2.2.2. Lack of enablement

Claims 85-94, 96-105 and new claims 106-111 are rejected under 35 U.S.C. 112, first paragraph, lack of enablement, for reasons made in the previous Office Actions, i.e., the final rejection and paper No.10. The reasons are reiterated herein.

The specification fails to describe a degree of toxicity and/or efficacy and its measurements. The disclosure is enabling for determining the presence and concentration of markers in a proteome, **but not their fragments. It is not a degree of toxicity or efficacy that is measured. What may be quantified is the ratio of**

levels of a marker protein after exposure to a new chemical and a standard or untreated control.

Examples presented by Applicant are silent about how to perform measurements of toxicity and efficacy, i.e. the disclosure is not enabling for a quantitative assay of toxicity/efficacy. The disclosure is enabling for visualizing the changes in the proteome induced by any agent and measuring the levels of the marker proteins. These measurements may be used further for calculating the ratio of the levels of the marker proteins after treatment with a tested drug and a standard drug or untreated control.

Applicants, themselves do not teach any standards that allow to determine whether a tested agent is toxic or efficient. Firstly, although the Applicants claim the use of one or more markers from 162 markers of claims 85 and 105 or one from 107 markers of claims 86 and 99, the specification does not teach which markers should be used for measurement of toxicity and which for measurement of efficacy. Applicants attention is turned to the fact that some markes are useless in following effects of a tested drug, because they do not belong to the pathway in which said drug is metabolized. The data in Table 1 reveals that there are only 3 out of 138 MSNs (2.17% of markers recorded), i.e., MSN 162 D-dopachrome tautomerase, MSN362 (not indentified in Table 1) and MSN413, which is cytosolic synthase of HMG-CoA, that are significantly changed in 5 out of 7 (71.4%) antilipemic agents. Thus, even these three markers could not be used in the claimed assay for all 7 antilipemic drugs taught by Applicants. In addition, the disclosure does not teach any calibration curve that would represent **a relationship between toxic effects measured by, for example,** increased

blood transaminases (see page 15, line 9) **and changes in the level of particular marker/markers in the proteome**. The disclosure also fails to teach any calibration curve for **efficacy of a drug, as for example** a relationship between the level of cholesterol in the blood after treatment with a particular drug and **a level of particular marker/markers in the proteome.**

The claimed subject matter is broad and includes unpredictable changes in the levels of proteins in the cell in response to the exposure to a drug or toxic agent. The quantity of some proteins may change in linear fashion; the amount of some proteins may be unaffected; some may disappear completely; some may change only after exposure to a certain threshold level of agent or may change in non-linear fashion. As such it would require undue experimentation to use any one or more protein markers to determine the efficiency or toxicity of a candidate agent absent guidance regarding how each marker changes in response to such agents and how the change correlate to toxicity and /or efficacy.

The specification enables one skilled in the art and the language of the claims refers to comparison of the proteome of the tissue exposed to a dose of the tested drug with that one exposed to a dose of the drug for which the characteristics of proteome is already known, or with proteome for unexposed control. Thus the disclosure enables quantifying the ratio of concentration of marker proteins after both exposures. However the specification is not enabling for measurements of toxicity or efficacy of any agent, including any antilipemic drug.

Traversing this rejection Applicants write on page 14, second paragraph of their REMARKS,

"The examiner has not established that blood transaminases levels can determine the **relative** toxicity of a drug. Thus, applicants have shown a superior toxicity measurement than that which the examiner contends to be enabled."

Applicants' argument as been fully considered, but is found not persuasive for the following reasons. To measure a toxic effect or toxicity an investigator has to defined it. When it is defined, a concentration of any marker that is shown to be correlated to toxic effect can be measured and reported as "absolute" i. e. expressed in units of weight per spot. The effect should be also related to non-treated control. Finally it may be, as Applicants emphasize, "relative", i.e. related to a sample treated with other agent of known or simultaneously determined effects. Determination of "absolute" or "relative" effects are just part of measurements and calculations, and there is nothing superior in determining a relative toxicity. Also, there is nothing inferior in determining "absolute" toxicity. As a matter of fact without a knowledge of "absolute" effects determination of "relative" toxicity, in case it is defined, would not be possible.

Furthermore, claims 90-94, 96-99 and 103-105 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method in which the amounts of a tested agent used are

a) "pharmaceutically appropriate,

b) "effective"

b) "greater than effective",

c) "toxic".

The specification does not teaches a "pharmaceutically appropriate, "effective", "greater than effective" or "toxic" dose for any agent, neither the specification teaches how to measure such amounts (doses) so that one skilled in the art could apply them as claimed.

A skilled artisan concludes, therefore, the claimed subject matter was not described in the specification in such full, clear, concise and exact terms as to enable any person skilled in the art, to which it pertains, to use the invention.

Traversing this rejection Applicants argue,

> "Several of the agents used in the specification are conventional FDA approved pharmaceuticals. These pharmaceuticals have well-established effective doses, which should provide much guidance as to the dosage questioned by the examiner. Furthermore, among the other locations in the specification, Example 1, first paragraph, provides the exact amount of lovastatin provided to each group of rats. Therefore, the specification provides sufficient guidance for

enablement of such descriptions and the rejection should be withdrawn."

Applicants' argument is found not persuasive, because providing lovostatin doses used in Example 1 is not enabling for

a) "pharmaceutically appropriate,

b) "effective"

b) "greater than effective",

c) "toxic"

amount of any agent or any antilipemic agent.

As to the conventional FDA approved pharmaceuticals, their well established effective dosages are not a guidance for any agent or any antilipemic agent as broadly claimed, but may be a guidance for compounds of similar chemical structure which are similarily metabolized.

2.3. 35 USC section 102

Claims 85-94, 96-97 and 98-105 were rejected under 35 U.S.C. 102(b) as being anticipated by Anderson at al. (A two-dimensional gel database of rat liver proteins useful in gene regulation and drug effects studies, *Electrophoresis*, **1991**, 12, 907-903) and Anderson et al. (An updated two-dimensional gel database of rat liver proteins useful in gene regulation and drug effect studies, *Electrophoresis,* **1995**, 16, 1977-1981). This rejection is withdrawn, because, as indicated by Applicants in their arguments on page 15, line 26 of the REMARKS, the claims are not directed to that

what has been taught by Anderson et al. in articles '91 and '95. Anderson at al. do not teach any method of determination of toxicity or efficacy of any agent or any antilipemic agent. After reconsideration of the claims and the articles the examiner concludes that the disclosure of the application is an expansion of what is taught by Anderson et al. '91. The specification of the instant application presents results of seeking for protein markers for drugs other than lovastatin or cholestyramine, or both applied together. Thus, Applicants, for the purpose of the present application, obtained proteomes of rat liver after treatment of animals with seven drugs listed above. Applicants define some new MSNs, but also include the data for lovastatin and cholysteramine from the '91 article. Applicants, however, do not describe and enable the method that is the subject of the claims.

4. Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (571) 272-0944. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (571) 272-0982. The fax phone number for this Group is (571) 273-0937.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.
Art Unit 1652
Patent Examiner

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